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(54) Transgenic non-human animals capable of producing heterologous antibodies

(57) The invention relates to transgenic non-human animals capable of producing heterologous antibodies, i.e., antibodies encoded by immunoglobulin heavy and light chain genes not normally found in the genome of that species of non-human animal. In one aspect of the invention, transgenes encoding unrearranged heterologous human immunoglobulin heavy and light chains are introduced into a non-human animal thereby forming a transgenic animal capable of producing antibodies encoded by human immunoglobulin genes. Such heterologous human antibodies are produced in B-cells which are thereafter immortalized, e.g., by fusing with an immortalizing cell line such as a myeloma or by manipulating such B-cells by other techniques to perpetuate a cell line capable of producing a monoclonal heterologous antibody. The invention also relates to heavy and light chain immunoglobulin transgenes for making such transgenic non-human animals as well as methods and vectors for disrupting endogenous immunoglobulin loci in the transgenic animal. The invention also includes methods to generate a synthetic immunoglobulin variable region gene segment repertoire used in transgene construction and methods to induce heterologous antibody production using animals containing heterologous rearranged or unrearranged heavy and light chain immunoglobulin transgenes.

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